*Is the prevention of anomalies as remote as you've always thought? We thought you'd enjoy this food for thought without fear of indigestion. You could even use this as source material for your next lay talk.*

# Human Congenital Anomalies.

## *Present Status of Knowledge*

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In the short space of a century the combined efforts of medical men and scientists in other fields have virtually overcome infections, at least the lethal types. The word "epidemiology" has taken on new meaning. Only rarely is epidemiology concerned now with infective patients, susceptible and immune people, and their inter-relationships. Epidemiologists are turning their attention to chronic diseases, degenerative conditions, and congenital malformations. Their study of environment and disease has taken on new parameters unheard of 100 years ago. Air pollution, the many kinds of radiation, chemicals used as preservatives and in packaging of foods, chemicals used as sprays to control insect invasion and as weed killers are all suspect in contributing to human disease.

There is good cause for hope in treating and even eliminating certain congenital anomalies. Both governmental and private agencies are pooling their resources in an all-out attack on the multiple problems involved. One certain result of the much-discussed Collaborative Study of Brain Deficiency will be an estimate, more accurate than any previously reached, of the true incidence of congenital disorders. The Children's Bureau is turning its attention seriously to this problem. The Association for Aid to Crippled Children is redoubling its interest in this field in which it has always been active. The National Foundation has initiated a program of research in etiology and prevention of congenital anomalies, and is attempting to educate the public in the medical and social aspects of these conditions, to train people in all related disciplines, and to care for a growing number of defective children. The United Cerebral

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Palsy Association through its research grants is fostering increasing knowledge in the many inter-related fields.

In view of the somewhat sudden focus on congenital anomalies, it is well to take stock now of what we know about the subject in the human species. Biologists and veterinary doctors have long been active in this field. Their experience serves as a background for human study. The seemingly unrelated fields of bacterial and viral genetics, transformation of bacteria, transduction, chemistry of nucleic acids, the thoroughly studied Drosophila melanogaster, and certain breeds of dogs with acetabular dysplasia all contribute to knowledge of human abnormalities. The reports of experimental work in teratogenesis are voluminous. It is a temptation which must be resisted, to transfer findings in lower animals to man. However, as satisfactory studies on that most difficult species, man, are completed, in almost every case, the results have been predicted from animal experiments. Man, as a species for experimental study is almost hopeless. He marries for love, not for eugenic reasons. His generation time is so slow that he often outlives the investigator. If he has kept careful track of his ancestors, and their health, he is useful if one knows how to take a genetic history. Experience with the 60 or so isolates in the United States has proved fruitful in this respect. Also the 22,000,000 ancestors of present-day Mormons documented individually in Salt Lake City form a splendid opportunity for pedigree analysis, but are useless with regard to their health records.

In the next 500 years, if the present trend to double the population every 40 years prevails, there will be 15,000,000,000,000 people on the earth, as estimated by Muller.[1] The actual number of congenital anomalies will increase in a parallel fashion, though it is doubtful if the mutation rate will of itself, increase. The Canadian Government recently asked Shaw for an estimate of the amount of blindness stemming from one person with aniridia (absent iris) 7 generations ago, who has died, leaving 77 affected descendants. From her studies, she has predicted the need for increasing the budget for aid to the blind in the province of New Brunswick.[2] One person with congenital telangiectasia, as reported by Hodgson et al.,[3] born in about 1860, has had 330 descendants with signs of the disease.

Radiation is high on the list of suspected teratogens in human beings. Studies have been of 2 types: short, high-dosage exposure, and long, low-level exposure. In the first instance, the follow-up studies of pregnancy during the Hiroshima and Nagasaki atom bomb explosions have proved to be unexpectedly difficult. Neel, Schull, Witkop, and others have found the high rate of consanguinity among the Japanese difficult to separate from the effects of the atom bomb. There was no previous estimate of congenital anomalies in the Japanese, but the rate of malformations among the controls, far distant from the bomb explosion, was twice as high as expected.[4] There was apparently a decrease in fertility of young married couples, but no proved increase in rate of congenital malformations, as a result of the sudden sharp dose of radiation. Obviously, observation of several generations will be necessary to determine the true effect of such dosage.

In an epidemiological study of certain areas of New York State where igneous rocks have a rather high background radiation, Gentry et al.[5] have described a significant increase in the number of congenitally malformed children born. Although this study has received much criticism, it has, at least, stimulated many other observations around the country.

On the other hand, more and more evidence is accumulating on the deleterious effect of radiation on human chromosomes, grown in tissue culture. Puck[6] has recently stated that there is *no* safe, threshold dose, and that *all* exposure to radiation is damaging to chromosomes. Fractionation of the chromatids, abnormal division, translocations, and the like can regularly be reproduced. Russell and Russell,[7] in Oak

Ridge, Tenn., have written recently that the time that the fertilized ovum is most sensitive to radiation is at its first division. They urge the use of diagnostic x-rays in young, married women only in the first 2 weeks after menstruation. Obviously, it is wise to avoid pelvic x-rays during the first 3 months of pregnancy Cowen and Geller [8] have recently described severe malformations in the brain of rats following radiation of the mothers during pregnancy. On the other hand, Copeland et al.,[9] in following up young women who had had treatment for dysmenorrhea by intracavitary radium, found only a significant decrease in fertility, but no malformed children among the few who were born.

Consanguinity is certainly suspect as a cause of congenital malformations. Each of us carries 2 to 10 deleterious genes, in the heterozygous state. Marrying close relatives obviously increases the possibility of abnormal children. The consanguinity rate for the entire United States is about 0.5%; in certain isolates in the southern Appalachian Mountains, it is 30%; in the non-isolate rural Applachian population it is about 3%, according to Herndon. If consanguinity is unavoidable, it is desirable to limit the size of the family, as Vaughn [10] suggests.

Innumerable chemical agents are used to produce abnormalities in animals. There are few data about human beings. These are reliable reports from Thiersch [11] who has used aminopterin, a folic-acid antagonist, to produce abortion in young women with active tuberculosis. If too small a dose of the chemical is administered, and abortion is not produced, there is a 100% incidence of abnormal offspring. His findings assume increased importance in the light of birth control measures. He feels strongly that the most successful method for birth control in underdeveloped countries is to treat the pregnant mother, early, with an ample dose of aminopterin. He believes this to be a much more practical method than expecting uneducated women to take certain steroid tablets 21 days every month, successful though that method is, in women who adhere faithfully to the schedule.

There are scattered cases in the literature suggesting a relationship between excessive cortisone during early pregnancy and abnormalities. These assume importance only because excessive cortisone administration to mice is a reproducible way to produce cleft palate. No thorough studies have been conducted in this field in human beings.

It is very difficult to do a proper, controlled study in the human species with regard to dietary deficiencies and congenital abnormalities. There is no real proof that an ample diet during the prenatal period is accompanied by healthier infants, though common sense dictates this relationship. Witkop,[12] in his study of dental abnormalities in racial isolates, came away with the feeling that "give them a good diet, and these abnormalities will diminish in spite of consanguinity."

McDonald,[13] Penrose,[14] and Stevenson [15] are especially active in epidemiological investigations in Great Britain and Ireland in relation to congenital malformations. There is a surprising incidence of anencephaly in Dublin, exceeding that in Paris by a ratio of 20:1. In Lyon, the condition is even more rare than in Paris. Also, in Africa anencephaly has rarely been reported, though this may be related to the quality of records. McDonald [13] has shown a statistically significant high frequency of abnormal children born of women in the lower socioeconomic level, Grade 5, engaged in heavy work, such as laundering.

Oxygen lack has been incriminated by Ingalls,[16] in animal experiments with low atmospheric pressures. There is no good evidence in human beings that there is such an association. His suggestion that anoxia is related to abnormalities rests on only 5 patients, 1 patient with a fever treated by tetracycline, 2 with acute anoxia, and 2 who had apparently uneventful anesthesia and operations in the first 3 months, all of whom had abnormal children. From this report, many physicians have recommended that high-altitude flights and opera-

tions with anesthesia be avoided in early pregnancy. Since Warkany [17] has shown that in rats salicylate poisoning can increase the rate of malformations, it is possible that the real culprit in Ingalls' experiments is asphyxia. Because of the unexpected, though rare asphyxial accidents occurring during operations and anesthesia, it is wise to avoid elective surgery during early pregnancy.

The relation of infectious agents and congenital malformations is steadily being clarified. Bacterial agents, such as (Diplococcus) Pneumococcus pneumoniae certainly increase fetal loss. There is some evidence that the infection toxoplasmosis, caused by a protozoon, in early pregnancy is associated with an increase in abnormal infants.[18] Töndury [19] has shown the effect of poliomyelitis infection in early pregnancy on the fetus. There is usually fetal death, with infection of the lens and of the nervous system. To date, no abnormal children have been born in association with polio infection in the mother.

Gregg, an Australian ophthalmologist, first pointed out in 1942 the association of rubella of the mother with eye defects in her offspring.[20] A summary of all the literature available indicates that at present about 30% of the live births following rubella in the mother are abnormal. In a recent paper, Gray [21] shows that 3 of 6 stillborn fetuses of mothers who had had rubella had abnormalities of the ear, eye, and heart. It seems logical, as a public health measure, to make sure that all high school girls have been exposed to the disease before marriage, although not all exposed persons become infected.

Two papers from Britain, by Coffey and Jessop,[22] and by Pleydell [23] indicate an association of Asian influenza with an increased number of birth defects. In neither of these was the diagnosis of the disease confirmed by virus isolation, or by antibody titer. In one study in this country, with such laboratory confirmation, there was not an increase in malformations.[24] Several such studies are in progress. It is unlikely that there will be an increased number of malformations as the result of any viral disease in which viremia cannot be proved.

One of the most fascinating aspects in the study of human malformations is the genetic aspect. The susceptibility or resistance to diseases is apparently heritable. The penetrance, or the frequency with which the deleterious gene makes its presence known, and the expression, or the severity of the symptoms of the disease, vary widely. Only 5% of those who carry the gene for diabetes mellitus in the heterozygous state develop clinical diabetes. The expression of the disease varies from an abnormal glucose tolerance curve, to blindness, or gangrene of the leg. So far, it is difficult to manipulate the penetrance of a gene, except by planned breeding experiments. It is much more possible to affect the expression of a disease by its early recognition and treatment.

The techniques of human genetics are many. More and more, a painstaking, genetic history of a patient reveals that apparently sporadic cases of malformations, or of rare diseases, are in reality hereditary. A pertinent example is the recent study of retinoblastoma, in Ohio, by Macklin.[25] On the other hand, completely mathematical formulae have been devised by Morton,[26] Steinberg,[27] and others for the inheritance patterns of different types, sex-linked recessive, autosomal dominant, and the like. Electronic computers have greatly simplified the mathematical work. Gene frequency can now be predicted in many conditions. This knowledge is especially useful in heredity counseling.

The almost daily advances in chemical research are fast narrowing the gap in biological interpretations. Deoxyribonucleic acid (DNA) is now widely recognized as the carrier of hereditary material, and the principal constituent of chromosomes. In some way, DNA transfers information to ribonucleic acid (RNA) in the nucleus, which then migrates into the cytoplasm and "instructs" the 20 or so amino acids how to synthesize proteins which are species-

specific. A mutation, which may produce anomalies, is probably identical with a variation in the sequence of purine-pyrimidine bases in nucleic acid. Every step in protein synthesis is aided by other proteins, enzymes. Deficiencies in certain enzymes which are heritable have been demonstrated in galactosemia, sensitivity to succinyl choline, primaquine sensitivity, and phenylketonuria.

Extensive studies of the hemoglobin molecule explain some of the hereditary deficiencies in this system. Ingram[28] first demonstrates that the hemoglobin in patients with sickle-cell anemia had an amino acid substitution, valine for glutamic acid. The actual sequence of amino acids in the alpha and beta chains of normal hemoglobin has almost been determined. The chemistry of A and B antigens in human blood is being clarified by Boyd.[29] Every one of these discoveries pertains to inborn errors of metabolism, with increasing frequency of identification of carriers, and possible substitution enzyme therapy to prevent serious sequelae, such as mental deficiency.

A final advance concerns chromosome identification, from tissue cultures of buccal mucous membrane, bone marrow, or other human tissues. At the date of this manuscript, there have been described almost 30 abnormalities of chromosome number or distribution. In April, 1960, an international committee met in Denver to decide, finally, on the proper numbering of chromosomes, 46 in number, after a 30-year error in believing that 48 was the proper number. Human chromosome abnormalities have now been shown to be associated with many cases of mental deficiency, sterility, skeletal defects, mongolism, and various human intersex conditions.

What hope is there to decrease human congenital anomalies and their effects? First, their early recognition after birth can lead to proper therapy. Many anomalies yield to surgery, if performed soon after birth. Phenylketonuria can be diagnosed in the first week after birth, appropriate diet prescribed, and mental deficiency prevented.

Second, by chemical methods, the recognition of heterozygotes carrying deleterious genes is becoming more and more possible. Knowledge of such gene aberrations will be useful in genetic counseling.

Third, cytologists are fast exploring nuclear transplantation, and in the near future will be transplanting chromosomes into recipient nuclei. In time their results will have a bearing on human reproduction.

Fourth, the nucleic acid chemists, many of whom are concerned with cancer chemotherapy, will add knowledge about the behavior of human DNA and RNA, and their inheritance.

Fifth, the genial battle between the empirical geneticists and the mathematical geneticists cannot help but produce useful results.

Finaliy, the decision to improve the human race rests with man himself. To quote Muller,[1] there is need "for finding practicable ways for controlling the production of reproductive cells, for storing them, and for transferring them."

## REFERENCES

1. Muller, H. G.: The Prospects of Genetic Change, Am. Scientist 47:551-562 (Dec.) 1959.

2. Shaw, M. W.: A Family Study of Aniridia, presented at American Society for Human Genetics, Memphis, Tenn. (April 28) 1960.

3. Hodgson, C. H.: Burchall, H. B.; Good, C. A., and Clagett, O. T.: Hereditary Hemorrhagic Telangiectasia, New England J. Med. 261: 625-636, (Sept. 24) 1959.

4. Schull, W. J., and Neel, J. V.: Atomic Bomb Exposure and the Pregnancies of Biologically Related Parents, Am. J. Pub. Health 49:1621-1629 (Dec.) 1959.

5. Gentry, J. T.: Parkhurst, E., and Bulin, G. V., Jr.: An Epidemiologic Study of Congenital Malformations in N.Y. State, Am. J. Pub. Health 49: 1-22 (April) 1959.

6. Puck, T. T., in Symposium on Methodology in Human Genetics, presented at University of Utah, May 13-14, 1960.

7. Russell, L. B., and Russell, W. L.: "Radiation Harms Embryo," Sc. News Letter 77:307 (May 14) 1960.

8. Cowen, D., and Geller, L. S.: Long Term Pathologic Effects of Prenatal X-Irradiation on the Central Nervous System of the Rat, J. Neuropath. & Exper. Neurol., to be published.

9. Copeland, W. E.; Nelson, P. K., and Payne, F. L.: Intrauterine Radiation for Dysfunctional Bleeding, Am. J. Obst. & Gynec. 73:615-623 (March) 1957.

10. Vaughn, V.: Address at the North Carolina Pediatric Society, Greensboro, N.C. (Oct.) 1959.

11. Thiersch, J. B.: Personal communication to the author.

12. Witkop, C. A.: Personal communication to the author.

13. McDonald, A. D.: Maternal Health and Congenital Defects: A Prospective Investigation, New England J. Med. 258:767-773 (April 17) 1958.

14. Penrose, L. S.: Genetics of Anencephaly, J. Ment. Defic. Res. 1:4-15 (July) 1957.

15. Stevenson, A. C.: The Load of Hereditary Defects in Human Populations, Radiation Res., Supp. 1, 1959, pp. 306-325.

16. Ingalls, T. H., and Philbrook, F. R.: Monstrosities Induced by Hypoxia, New England J. Med. 259:558-564 (Sept. 18) 1958.

17. Warkany, J., and Takacs, E.: Experimental Production of Congenital Malformations in Rats by Salicylate Poisoning, Am. J. Path. 35:315-331 (March-April) 1959.

18. Feldman, H. A.: Toxoplasmosis, Pediatrics 22:559-574 (Sept.) 1958.

19. Töndury, G.: Erkrankt der Fetus bei Poliomyelitis in Gravidate, Schweiz. med. Wchnschr. 87:809-812 (June 29) 1957.

20. Gregg, N. M.: Congenital Cataract Following German Measles in Mother, Tr. Ophth. Soc. Australia 3:35-46, 1942.

21. Gray, J. E.: Rubella and Pregnancy, Brit. M.J. Pediat. 1388-1390 (May 7) 1960.

22. Coffey, V., and Jessop, W. J. E.: Maternal Influenza and Congenital Deformities, Lancet 2: 935-938 (Nov. 28) 1959.

23. Pleydell, M. J.: Anencephaly and Other Congenital Anomalies, Brit. M.J. 309-315 (Jan. 30) 1960.

24. Wilson, M. G.; Heins, H. L.; Imagawa, D. T., and Adams, J. M.: Teratogenic Effects of Asian Influenza, J.A.M.A. 171:638-641 (Oct. 10) 1959.

25. Macklin, M.: A Study of Retinoblastoma in Ohio, Am. J. Human Genetics 12:1-43 (March) 1960.

26. Morton, N. E., in Symposium on Methodology in Human Genetics, presented at University of Utah, May, 1960.

27. Steinberg, A. G., in Symposium on Methodology in Human Genetics, presented at University of Utah (May) 1960.

28. Ingram, V. M.: The Thread of Life, television film, British Broadcasting Company, 1960.

29. Boyd, W. C., in Symposium on Methodology in Human Genetics, presented at University of Utah (May) 1960.